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T-cell–redirecting bispecific antibodies in multiple myeloma: a revolution?

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Bispecific antibodies are monoclonal antibodies targeting both a surface molecule on the malignant plasma cells and CD3 on T cells, leading to tumor cell death by activated T cells. Bispecific antibodies targeting B-cell maturation antigen, GPRC5D or FcRH5, demonstrated promising efficacy with favorable safety profile in patients with triple-class refractory multiple myeloma. This novel immunotherapeutic modality will likely change the treatment paradigm in the coming years.

Introduction

The outcome of patients with relapsed/refractory multiple myeloma (RRMM) remains challenging. Patients with triple-class exposed RRRM (prior exposure to immunomodulatory drugs, proteasome inhibitor, and anti-CD38 monoclonal antibodies) have a median overall survival (OS) of nearly 1 year.[1] Effective novel therapies are therefore needed. The most promising developments include novel immunotherapeutic approaches such as chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies (BispAbs).[2,3] The CAR T-cell therapy ide-cabtagene vicleucel (ide-cel) has been approved for triple-class exposed patients with MM refractory to their last therapy.[4] Across all target doses, the median progression-free survival (PFS) was 8.6 months, and the median OS was 24.8 months.[5] Ciltacabtagene autoleucel (cilta-cel), a CAR T-cell therapy with 2 B-cell maturation antigen (BCMA)–targeting single-domain antibodies showing a 97.9% response rate and 18-month PFS and OS rates of 66.0% and 80.9%, respectively,[6] is also approved for triple-class–exposed patients. One important challenge with CAR T-cell therapy is the lengthy (6-8 weeks) and individualized manufacturing process, which might not be feasible for patients with aggressive disease course.[4,5] On the opposite side, BispAbs are readily available off-the-shelf products. Ongoing phase 1/2 clinical trials using different constructs, with different targets on myeloma cells, are showing a favorable safety profile with high response rates in heavily pretreated patients.

Approaching bispecific antibody engineering

A BispAb is able to bind to an antigen on the tumor cell and to another antigen on T-cell lymphocyte to redirect these immune cells toward malignant cells.[2,7-18] This immunologic synapse formation is followed by T-cell activation and degranulation and the release of granzymes and perforins, leading to tumor cell lysis. BispAb constructs promote sustained T-cell activation, leading to polyclonal expansion of memory T cells.[10] BispAbs act independently of major histocompatibility complex or T-cell receptor specificity.[2,7-18] Different formats of bispecific T-cell–redirecting antibodies have been developed. Bispecific T-cell engager (BiTE) consists of a single-chain fragment variable for binding the target antigen on the malignant cell and another single-chain fragment variable for binding a T cell, the 2 being connected by a linker peptide.[2,7-18] BispAbs lacking an Fc region more easily penetrate tumors due to their small size but are associated with short half-life requiring frequent or continuous infusion.[7-18] BispAbs with Fc domain (full size) creating an IgG-like molecule have an extended half-life, allowing intermittent dosing, Fc-mediated effector functions, and potential subcutaneous administration.[7-18] Additionally, it is possible to build IgG-like TrispAbs with additional binding sites targeting T-cell and 2 distinct plasma cell antigens or a single myeloma antigen and 2 distinct antigens of the immune effector cell.[19-21]

Myeloma cell targets

The optimal target is an antigen constantly expressed by myeloma cells with minimal expression by healthy tissues to minimize toxicity. Numerous potential myeloma cell targets are under evaluation for clinical development of BispAbs, such as CD38, CD138, CD200, and SLAMF7, but as of the writing of this article, clinical data are available for BCMA, GPRC5D, and FcRH5.[2,7-9,14,18,22]

BCMA, or CD269, is currently the major target for BispAbs, with at least 8 different compounds in preclinical/clinical development to date.[2,7-9,14,18,22] BCMA, a type III transmembrane glycoprotein belonging to the tumor necrosis factor receptor superfamily, regulates B-cell proliferation, maturation, survival, and differentiation to plasma cells.[23] BCMA is expressed at high levels on both malignant and normal plasma cells yet remains undetectable in hematopoietic stem cells and most nonhematologic tissues.[23-25] GPRC5D is a transmembrane orphan receptor of the G protein-coupled receptor family class C group 5 member D whose functions are poorly characterized.[26-29] It is highly

Table 1. Safety and efficacy of BispAbs

	CC-93269[38] n = 30	AMG701[39] N = 75	Teclistamab[39] n = 159	Elranatamab[40] n = 50	RENG5458[41] n = 68	Tnb-383B[42] n = 103	Talquetamab[43] n = 95	Cevostamab[44] n = 160
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	GPRC5D	FcRH5
Phase	1	1	1/2	1	1/2	1	1	1
Administration	IV*	IV weekly	SC weekly	SC Q2W	IV weekly, then Q2W	IV Q3W	SC weekly or Q2W	IV Q3W
Median number of prior regimens	5 (3-13)	6 (1-25)	5 (2-15)	6	5 (2-17)	5 (1-15)	NR	6 (2-18)
Median age, y	64 (42-78)	63	64 (33-84)	64 (32-86)	64 (41-81)	67 (35-88)	61 (46-84)	64 (33-82)
Triple refractory (%)	NR	68	77	98	100	62	81	85
RP2D	Not reached	Not reported	1.5 mg/kg weekly	1 mg/kg	NR	60 mg Q3W	405 μg/kg weekly or 800 μg/kg Q2W	NR
CRS, grade ≥3 (%)	77, 4	61, 7	67, 1	83, 0	38, 0	52, 3	73, 3 at 405 μg/kg weekly 78, 0 at 800 μg/kg Q2W	80, 1
Median duration of CRS (d)	NR	2	2 (1-9)	2	NR	NR	NR	2
Median time to onset of CRS (d)	NR	NR	2 (1-6)	NR	NR	1	NR	1
Neurotoxicity, grade ≥3 (%)	NR	8, 0	2.5, 0	NR	NR, 0	NR	NR	13.1, 3.8
Neutropenia, grade ≥3 (%)	NR, 43	23, NR	53, 45	64, 60	16, 13	17, NR	67, 60 at 405 μg/kg weekly 44, 35 at 800 μg/kg Q2W	15, 13.8
Anemia, grade ≥3 (%)	NR, 37	43, NR	41, 27	55, 38	NR	9, NR	NR	31.9, 21.9
Thrombocytopenia, grade ≥3 (%)	NR, 17	20, NR	33, 18	52, 31	NR	14, NR	NR	NR
Infections, grade ≥3 (%)	NR, 30	NR, 17	45, 22.5[37]	NR	NR	28, NR	37, NR at 405 μg/kg weekly 13, NR at 800 μg/kg Q2W	42.5, 18.8

DOR, duration of response; NR, not reported; ORR, overall response rate; Q2W, every 2 weeks; Q3W, every 3 weeks; RP2D, recommended phase 2 dose; SC, subcutaneous.

*On days D1, 8, 15, and 22 for cycles (C) 1-3; D1 and 15 for C4-6; and on D1 for C7 and beyond, all in 28-day cycles for up to 2 years.

Table 1. (continued)

	CC-93269[38] n = 30	AMG701[39] N = 75	Teclistamab[39] n = 159	Elranatamab[40] n = 50	RENG5458[41] n = 68	Tnb-383B[42] n = 103	Talquetamab[43] n = 95	Cevostamab[44] n = 160
ORR across all dose levels (%)	43	23.6	NR	NR	NR	NR	NR	NR
ORR at RP2D or efficacious dose range (%)	89 (9/10 at 10 mg)	83 (5/6 at 9 mg)	65	70	73.3 at 96 mg + 200 mg dose levels	64 for cohorts ≥ 40 mg	70 at 405 µg/kg weekly 71 at 800 µg/kg Q2W	36.7 at 90 mg 54.5 at 160 mg
Median time to response (d)	29	29	29	22	NR	NR	NR	29
DOR	5.3 to 40.6 wk	3.8 mo (1.9, 7.4)	6 mo: 90%	95% CI at 6 mo: 92.3% (56.7-98.9)	DOR ≥ 8 mo: 92.1%	NR	6 mo: 67% at 405 µg/kg weekly	Median: 15.6 mo (95% CI: 6.4-21.6)

DOR, duration of response; NR, not reported; ORR, overall response rate; Q2W, every 2 weeks; Q3W, every 3 weeks; RP2D, recommended phase 2 dose; SC, subcutaneous.
*On days D1, 8, 15, and 22 for cycles (C) 1-3; D1 and 15 for C4-6; and on D1 for C7 and beyond, all in 28-day cycles for up to 2 years.

expressed on myeloma cells (no expression on other hematopoietic cells), as well as keratinized structures, including hair shaft, nail, and central region of the tongue.[26-29] GPRC5D overexpression has been correlated with adverse prognosis in MM.[30] Of note, plasma cells of patients with MM exhibit differential expression of both BCMA and GPRC5D, consistent with data suggesting that BCMA and GPRC5D may be independently regulated in MM cells.[31] GPRC5D represents a novel and attractive target for MM, and 2 BispAbs are currently being evaluated in preclinical[27] or clinical studies.[28]

The Fc receptor-homolog 5 (FcRH5), also designated as CD307, FcRL5, and IRTA2, is a membrane protein from the immunoglobulin superfamily implicated in proliferation and isotype expression in the development of antigen-primed B cells.[32] Its expression is restricted to the B-cell lineage with increased expression in mature B cells and plasma cells.[33] FcRH5 expression has also been shown to be higher in myeloma cells in comparison with normal plasma cells.[32,33] Interestingly, the FcRH5 gene is located in the chromosome region 1q21.[34] Some data suggest that the 1q21 gain can lead to FcRH5 overexpression in patients with high-risk MM.[34-36] Therefore, FcRH5 is an interesting target for the BispAb cevostamab.[2,3,7-15,18,22]

Clinical results

Only 2 phase 1 trials have been reported in peer-reviewed publications to date, the first investigating anti-BCMA BiTE molecule AMG 420[37] (whose development has been discontinued due to inadequate PK), and the second investigating teclistamab, a BCMA × CD3 T-cell–redirecting BispAb, in heavily pretreated patients with RRMM.[38] However, data from 8 early phase trials have been already reported in conference proceedings that have enrolled 485 patients treated with BCMA-BispAb,[39-44] 95 treated with GPRC5D-BispAb,[45] and 160 treated with FcRH5-BispAB,[46] respectively.

Safety

The most common adverse events (AEs), similar across trials, are summarized (Table 1) from 740 heavily pretreated patients with a median age of 64 years.[39-46]

Cytokine release syndrome

Cytokine release syndrome (CRS) is an acute systemic inflammatory syndrome characterized by the activation of T cells and other immune effector cells leading to significant cytokine release, whose severity is related to disease burden and dose of immunotherapy.[47] Step-up dosing with progressively increasing doses administered during the week prior to first full dose was used in most studies to mitigate CRS intensity. Incidence of CRS ranged from 38% to 83%, including only 0% to 4% grade ≥3 CRS. Across all studies, the use of tocilizumab (which should be considered as first treatment) and corticosteroids (which should be added in case of limited improvement following a repeated dose of anti–interleukin-6 therapy) to treat CRS was approximately 40% and 20%, respectively. Median time to CRS ranged from 12 to 48 hours, with earlier event (24 hours) with intravenously administered BispAbsin compared with subcutaneously administered (2 days) BispAbs. The median CRS duration

Table 2. Ongoing studies evaluating BispAbs in multiple myeloma

Study	Population	Phase	Treatment
CD3 × BCMA			
NCT04557098 (MajesTEC-1)	RRMM	1-2	Teclistamab
NCT04722146 (MajesTEC-2)	RRMM and NDMM	1b	Teclistamab in combination with - dara pom - dara len - dara btz len - len - nirogacestat
NCT05083169 (MajesTEC-3)	RRMM	3 randomized	Teclistamab dara vs DPd/DVd
NCT04108195 (TRIMM-2)	RRMM	1b	Teclistamab in combination with - dara - dara pom
NCT04586426	RRMM	1b	Teclistamab in combination with - talquetamab - talquetamab dara
NCT05243797 (MajesTEC-4)	NDMM (maintenance)	3 randomized	Teclistamab len vs len
NCT05231629 (Master-2)	NDMM	3 randomized	Teclistamab dara
NCT03269136 (MAGNETISMM-1)	RRMM	1	Elranatamab
NCT04649359 (MAGNETISMM-3)	RRMM	2	Elranatamab
NCT05090566 (MAGNETISMM-4)	RRMM	1b-2	Elranatamab + nirogacestat
NCT05020236 (MAGNETISMM-5)	RRMM	3	Elranatamab dara vs DPd
NCT05137054	RRMM	1b	REGN5458 in combination with - carfilzomib - len dex - btz dex - dara dex
NCT03933735	RRMM	1	TNB-383B
NCT04184050	RRMM	1-2	HPN217 (trispecific BCMA × CD3 × albumin)
NCT04735575	RRMM	1-2	EMB-06
GPRC5D × CD3			
NCT03399799 (MONUMENTAL-1)	RRMM	1	Talquetamab
TRIMM-2 NCT04108195	RRMM	1b	Talquetamab dara Talquetamab dara pom
NCT05050097 (MONUMENTAL-2)	RRMM	1b	Talquetamab in combination with - carfilzomib - carfilzomib dara - len - len dara - pom
FCRH5 × CD3			
NCT03275103 (GRACE)	RRMM	1	Cevostamab
CD38 × CD3			
NCT03309111	RRMM	1	ISB 1342
NCT05011097	RRMM	1	Y150

btz, bortezomib; dara, daratumumab; DPd, daratumumab-pomalidomide-dexamethasone; DVd, daratumumab-bortezomib-dexamethasone; len, lenalidomide; NDMM, newly diagnosed multiple myeloma; pom, pomalidomide.

ranged from 12 to 48 hours. CRS events are generally restricted to the first cycle, and all patients but one[39] recovered with no sequelae.

Neurotoxicity

Any-grade neurotoxicity ranged from 2% to 13%, including 0% to 4% grade ≥3 events. Symptoms included headache, confusion, aphasia, cognitive disorder, and encephalopathy. Neurologic symptoms were commonly concomitant of CRS and fully resolved after CRS therapy.

Hematologic effects

Hematologic side effects across all trials included anemia (any grade 9% to 41%; grade ≥3 21.9% to 38%), neutropenia (any grade 15% to 67%; grade ≥3 13% to 60%), and thrombocytopenia (any grade 14% to 33%; grade ≥3 17% to 31%). The origin of cytopenias is not yet well understood considering the mechanism of action of BispAb. Therefore, 1 hypothesis involves a "bystander" effect from the cytokine release and destruction of plasma cells in the bone marrow.

Infections

Infection was observed in 13% to 52% of patients, with grade ≥3 in 18% to 30%.[38-46] In this heavily pretreated population with severe immunosuppression and profound hypogammaglobulinemia, the source, type, and time to onset of infection were not widely reported. Nevertheless, a recent series on 36 patients treated with BispAbs suggests a higher rate of infections than CAR-T due to continuous therapy.[48] An important issue in the COVID-19 era is the lack of response to vaccines. A recent study from the Mount Sinai NY group showed, in a small number of cases, that patients receiving BCMA-targeted therapy, including BispAbs, had impaired T-cell response and lower severe acute respiratory syndrome coronavirus 2 spike-binding IgG antibody levels after 2 doses of vaccine compared with patients receiving other antimyeloma therapy.[49] More data with longer follow-up are needed before making appropriate recommendations for screening, monitoring, and prophylaxis of infections in patients receiving BispAbs.[50]

Other specific toxicity

The anti-GPRC5D talquetamab antibody was unique in causing dysgeusia (60%; grade 2: 29%), skin-related AEs (77%; all grade 1/2) and nail disorders (30%)[45] in conjunction with the GPRC5D expression on hard keratinized structures. The dermatologic and oral events are mostly low grade and rarely require dose modifications. AEs have been manageable with early and consistent supportive care.[51]

Efficacy

Although safety and dose identification are the primary objectives of these phase I trials,[38-46] preliminary efficacy data are available for the most active dose cohorts (Table 1). Responses were rapid, with a median time to first response of 4 weeks. For these heavily pretreated (median number of prior therapies: 6; triple-class refractory: 81%) patients treated across the efficacious dose range, the overall response rates ranged from 36.7% to 89%, with a dose-dependent increase in clinical efficacy. Minimal disease negativity data were immature. Because the median follow-up periods from these early phase studies are still short, the median duration of response has not been reached. Although efficacy data need to be confirmed in larger numbers of patients, these preliminary response rates compare favorably with recently approved drugs in MM for triple-class exposed/refractory patients, such as selinexor[52] or belantamab-mafodotin.[53] No data are available yet in specific populations of interest (ie, elderly/frail patients and patients with high-risk cytogenetics, renal failure, or extramedullary disease).

Mechanisms of resistance

Resistance may be related to tumor-related features, T-cell characteristics, and immunosuppressive microenvironment. T-cell exhaustion is a feature of MM that may be potentialized by BispAbs therapy.[36,54,55] Dysregulation of regulatory T cells, tumor-associated macrophages, and myeloid-derived suppressor cells have also been described as resistance mechanisms.[8,9,56-58] Recently, a case of a biallelic *BCMA* gene deletion was described as a cause of acquired-resistance to a BCMA-specific BispAb.[59] Furthermore, by using whole-genome sequencing data, the authors demonstrated that genomic alterations in genes encoding immunotherapy targets were preexisting in some patients before immunotherapy and could be used as biomarker of response.[59]

Future developments

Two strategies are under evaluation to improve efficacy further on: combination therapies and earlier use of BispAbs (Table 2). There is a strong rationale for combining BispAbs with CD38 antibodies. Daratumumab impacts immune cell populations (ie, increasing helper and cytotoxic T cells and decreasing suppressive $CD38^{+}$ immunoregulatory cells).[60] Preclinical studies showed that addition of daratumumab enhanced teclistamab[56]- and talquetamab[61]-mediated lysis of MM cells, suggesting the combination may also increase clinical activity in patients with RRMM. Preliminary data from the phase 1b multicohort study TRIMM-2 (combination of talquetamab[62] or teclistamab[63] with daratumumab) have been recently reported and showed that the 2 combinations were well tolerated and demonstrated promising efficacy in patients with RRMM. Because of their ability to promote T-cell activity, there is also a strong rationale to combine BispAbs with immunomodulatory drugs. Due to the high mutational burden of MM and the multiclonal nature of the tumor, a logical approach could be to combine BispAbs targeting different antigens. An ongoing study (#NCT04586426) is already evaluating teclistamab plus talquetamab in advanced patients. T-cell exhaustion as a potential mechanism favoring progression in MM supports the use of BispAbs earlier in the course of the disease.[64,65] Moreover, the frequency of deletions and mutations in genes encoding immunotherapy targets is higher in patients with very advanced disease.[59] Ongoing trials are already testing BispAbs in combination with pomalidomide

or carfilzomib at earlier lines of therapy, and other trials are planning to use these agents as part of frontline therapy.

Conclusions

BispAbs represent a promising new class of agents for MM and will probably become a standard of care in the near future. Their safety profile is favorable, allowing ambulatory use. Additional data are needed to further evaluate long-term toxicities and the risk of infection more specifically. BispAbs are off-the-shelf products and allow rapid responses, which is crucial for patients with rapidly progressive disease. More data for PFS and OS are requested, but their efficacy is highly promising. With the recent approval of BCMA-directed CAR-T therapy in MM, many issues are arising about the use of BispAbs versus CAR-T. The choice between the two modalities depends on various practical considerations: efficacy, disease status, age, comorbidities, product availability, distance from an academic center, and optimal sequencing (prior exposure to BCMA therapy). Finally, BispAbs might be easily incorporated with currently approved myeloma therapies in earlier lines of treatment to increase efficacy as we continue the quest for cure.

Authorship

Contribution: P.M. and C.T. wrote the manuscript.

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Footnote

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